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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HENLEY III, RAYMOND J	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 12/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/696,256	AZROLAN ET AL.	
	Examiner	Art Unit	
	Raymond J. Henley III	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

CLAIMS 15-27 ARE PRESENTED FOR EXAMINATION

Applicants' amendment filed September 21, 2005 has been received and entered into the application. Accordingly, claims 1-15 have been canceled and the disclosure at page 1 has been amended.

In light of the above amendments, the rejection of claims 1, 2, 8 and 9 are rejected under 35 U.S.C. 102(b), the rejection of claims 1-14 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,670,355 and the objection to the specification, as set forth in the previous Office action dated April 22, 2005, are each withdrawn.

Specification

The disclosure is objected to because of the following informality:

In Applicants' amendment to the specification, line 2, one of the terms "of" in the expression ---of of--- must be canceled.

Appropriate correction is required.

Grounds of Rejection

The grounds of rejection set forth below are essentially the same as set forth in the previous Office action except for that references to the requirements in claims 1, 2, 8 and 9 under 35 U.S.C. §§ 102(b)/103 made in the previous Office action have been withdrawn. For example, the reference Wright et al. (U.S. Patent No. 6,585,764) was employed to show the obviousness of employing the claimed actives for coronary artery disease (CAD). The present claims do not

include such a requirement and thus this reference, while still being of record, is no longer relied on.

Claim Rejection - 35 USC § 103

Claims 1-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Morris et al. (U.S. Patent No. 5,516,781, cited by Applicants, reference "TT") or Mitchell et al. (U.S. Patent No. 5,288,711, cited by Applicants, reference "Z"), in view of Schuler et al. (U.S. Patent No. 6,384,046), Somers (U.S. Patent No. 6,121,319, cited by Applicants, reference "XX"), Applicants' acknowledgment at page 5, line 10 – page 6, line 22 of the present specification and The Merck Manual of Diagnosis and Therapy ("Merck", cited by Applicants, reference "OOO").

Morris et al. (U.S. Patent No. 5,516,781, cited by Applicants, reference "TT") or Mitchell et al. (U.S. Patent No. 5,288,711, cited by Applicants, reference "Z") who teach methods for the treatment of hyperproliferative vascular disease in a mammal (see the abstract of either patent) which comprises the administration of rapamycin alone (Morris et al., last two lines of the abstract) or rapamycin and heparin (Mitchell et al., last line of the abstract). Mitchell et al. further teach that vascular injury, including injury attributed to autoimmune disorders or alloimmune related disorders or *atherosclerosis* may be treated, (emphasis added), (col. 3, lines 38-40 and 43). Morris et al also expressly disclose that atherosclerosis may be treated (col. 1, lines 45-60).

Steadman's Medical Dictionary (cited by the Examiner) defines atherosclerosis to mean "arteriosclerosis characterized by irregularly distributed lipid deposits in the intima of large and medium-sized arteries; such deposits are associated with fibrosis and calcification" (page 148, col. 1). Therefore, the references' disclosure of atherosclerosis is deemed to have placed the

concept of "treating or inhibiting lipid deposition or accumulation in vascular wall in a mammal (claim 22) in the possession of the public.

The differences between the above and the claimed subject matter lies in that neither Morris et al. nor Mitchell et al. disclose:

(i) the presently claimed rapamycin derivatives as being useful in the place of rapamycin (claims 17-20 and 24-27);

(ii) the additional use of the pharmaceutical agents of present claims 14 and 21; and

(iii) the inhibition of stroke, multiinfarct dementia (present claim 15) or accumulation of lipid in a vascular wall (present claim 22).

However, the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains because:

(i). Schuler et al. disclose treatments for hyperproliferative vascular diseases, including atherosclerosis, wherein rapamycin derivatives are effectively employed (see Schuler et al. at the abstract; col. 1, line 5 – col. 2, line 36, col. 3, lines 41-46). Given the combined teaches of Morris et al. or Mitchell et al. and Schuler et al., it is believed that one of ordinary skill in the art would have been imbued with a reasonable expectation that not only could rapamycin be administered, but the presently claimed rapamycin derivatives as well. One of such skill would have been motivated to employ the presently claimed rapamycin derivatives for the same or a similar purpose as rapamycin because from Applicants' acknowledgment at page 5, line 10 – page 6, line 22 of the present specification, such derivatives were known to the skilled artisan

and as such, would have been expected to provide at least similar results to those achieved for rapamycin itself.

(ii) Somers et al. teach that the pharmaceutical agents of present claims 14 or 21 were known to be useful for treating vascular diseases such as those of the primary references such as atherosclerosis (see col. 6, lines 28-29 and col. 8, line 62 – col. 9, line 6) and it has been held that it is considered prima facie obvious to have combined two or more ingredients each of which was known to be useful for the same purpose in order to form a third composition that is useful for the very same purpose. The idea for combining them flows logically from their have been used separately. See *In re Kerkhoven*, 205 U.S.P.Q. 1069 (CCPA 1980) and the cases cited therein. The skilled artisan would have been motivated to combine such ingredients in order to achieve *at least* additive results and to provide the individual being treated with the most convenient, effective therapy possible.

(iii) As discussed above, Morris et al. teach that rapamycin atherosclerosis. Such disease includes the migration and proliferation of vascular smooth muscle cells and such plays a "crucial role in the pathogenesis of atherosclerosis" (see Morris et al. at col. 1, lines 49-51). Morris et al. further teach that atherosclerotic lesions include massive accumulation of *lipid laden* foam cells derived from monocyte/macrophage and smooth muscle cells (col. 1, lines 51-53). Accordingly, one of ordinary skill in the art would have recognized that because rapamycin was effective in the treatment of atherosclerosis, it would also be effective for inhibiting or treating lipid deposition or accumulation in a vascular wall because atherosclerosis is characterized by lipid accumulation.

Respecting the treatment of stroke or multiinfarct dementia, Merck teaches that cerebrovascular disease, including ischemic syndromes, i.e., strokes (page 1324, col. 1) and transient ischemic attacks ("TIAs") (page 1324, col. 2, last section – page 1327) were known to have a causal association with hyperproliferative vascular diseases, i.e., caused by "thrombosis or emboli from an atherosclerotic plaque..." (page 1324, col. 1, lines 7-8 under the heading "Etiology and Pathophysiology"). Merck further teaches that "Most TIAs are due to cerebral emboli arising from plaques or atherosclerotic ulcers involving the carotid or vertebral arteries in the neck." (page 1326, col. 1, lines 1-3). Therefor, the inhibition or treatment for atherosclerosis would have been recognized as also being an effective inhibition for the development of a stroke. Also, regarding multiinfarct dementia, because it involves multiple infarcts and an "infarct" is an element of a stroke (Merck at page 1325, lines 1-2), it would have also been obvious that the development of multiinfarct dementia could also be inhibited.

Accordingly, for the above reasons, the claims are deemed properly rejected.

Applicants' Remarks

Applicants' remarks that the above does not support a conclusion of obviousness under 35 U.S.C. § 103 at pages 5-8 of their amendment have been carefully considered, but fail to persuade the Examiner of error in his determination of obviousness.

The essence of Applicants' arguments appear at page 5, first full paragraph under in section 'II". That is:

> "In summary, there is no motivation in the art to combine the teachings of the document. In fact, the teachings of Mitchell (which requires a component not recited in the claims) and Somers (which contains no teaching of a rapamycin) would lead one of skill in the art away from such a combination and any expectation of success.

However, even if combined, the cited combination fails to suggest the present invention."

In response, the Examiner notes that Somers was relied on only for the teaching that it would have been obvious to employ the additional actives of claim 21 and has been properly combined with the remaining references. Further, the interpretation of the references presented by the Examiner are valid and, contrary to Applicants' opinion, is believed to have been such that one of ordinary skill in the art would have been lead to a conclusion that the claimed subject matter would have been obvious.

At page 6 of their amendment, Applicants have urged that neither Morris, Mitchell, Wright or Schuler assess the ability of the compounds to prevent lipid deposition or accumulation by the direct effect on plasma lipids, i.e., only the anti-hyperproliferative effect of rapamycin following direct injury to cell walls is addressed. Further, Applicants state that the art fails to address the accumulation of lipids in the walls of blood vessels is an important aspect of the atherosclerotic process. Also, Applicants' urge that the data contained in the present disclosure shows a positive effect of rapamycin on plasma lipids and "supports the medical use as expressed in claim 1", (page 6 of the amendment, fourth full paragraph).

In response, the Examiner wishes to point out that **claim 1 has been canceled**. Thus, these comments of Applicants are not germane to the present rejection. Insofar as claims 15-21 are concerned, (claim 15 being directed to inhibiting stroke or multiinfarct dementia), it is the Examiner's position that inhibiting stroke or multiinfarct dementia would have been obvious rests on a conclusion the skilled artisan would have recognized the nexus between such conditions and atherosclerosis and that the treatment of atherosclerosis with rapamycin compounds would ultimately lead to a treatment for inhibiting stroke or multiinfarct dementia

(see previous Office action at page 7, first full paragraph). Applicants at page 8 point out that "while the ability of rapamycin to treat cellular hyperproliferation was described...the ability of rapamycin to prevent lipid accumulation was previously unrecognized." (response at page 8). While such may have been unrecognized, such does not alter the obviousness of the presently claimed subject matter because the present rejection is under §103 rather than §102 of 35 U.S.C.

Also, respecting Applicant's comments that the art did not recognized rapamycin's effect as did Applicants (e.g., see Applicants' amendment at page 6, last full paragraph), such also does not render the present claimed subject matter obvious because (i) as noted above, claim 1 has been canceled; and (ii) it is immaterial that Applicants have discovered a new reason why the conditions of the claims may be treated: the prior art makes obvious what Applicants are ultimately doing. To put it in another way, the fact that Applicants have recognized another advantage which would flow naturally from following the suggestion of the prior art or that the objective of the prior art could be accomplished by other means cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Applicants' remarks concerning the Somer, Morris, Mitchell and Wright references at page 7 of their amendment have also been considered, but are not persuasive. It is well recognized that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Accordingly, the claims are deemed properly rejected.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Non-Provisional

I Claim 22 remains rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8 and 9 of U.S. Patent No. 6,680,330, (Zhu et al., cited by the Examiner), which has a common assignee with the present application, in view of Wright et al. (U.S. Patent No. 6,585,764, cited by the Examiner) and Mitchell et al. (U.S. Patent No. 5,288,711, cited by Applicants, reference "Z").

The differences between the present claims and the patented claims lies in that restenosis is being treated or inhibited in the patented claims with a dialdehyde rapamycin compound, while the present claims do not expressly set forth either a dialdehyde rapamycin compound or restenosis as a therapeutic objective.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims recite "a rapamycin" and thus includes rapamycin compounds in general which would have included the aldehyde derivative form of rapamycin of the patented claims. Also, the present claims recite the treatment or inhibition of cardiovascular

disease or the treatment of atherosclerosis in general and would have included a treatment for restenosis because the defining characteristics of restenosis clearly indicate that it may be considered a type of cardiovascular disease which may be associated with atherosclerosis and thus, the treatment of restenosis would be included in the scope of the present claims. In particular, Wright et al. (U.S. Patent No. 6,585,764), teaches the following regarding the characteristics of restenosis: "Re-narrowing [restenosis] of an atherosclerotic coronary artery after percutaneous angioplasty (PTCA) occurs in 10-50% of patient undergoing this procedure and subsequently requires either further angioplasty or coronary artery bypass graft." (col. 1, lines 23-27).

Present claim 22 requires that lipid deposition or accumulation be treated or inhibited. This requirement is believed to be met by the patented claims because restenosis occurs in a vessel that may be atherosclerotic, which would indicate that lipid accumulation in the vessel walls would be present (see Mitchell et al. at col. 1, lines 58-68). While the treatment of restenosis does not directly involve the lipid deposits, such deposits would indirectly be "treated" through the treatment of the restenosis thus meeting the present claim requirement.

Applicants' Arguments

Applicants' arguments at pages 8-9 have been carefully considered, but fail to persuade the Examiner of error.

In particular, each of U.S. Patent No. 6,680,330, (Zhu et al., cited by the Examiner), which has a common assignee with the present application, in view of Wright et al. (U.S. Patent No. 6,585,764, cited by the Examiner) and Mitchell et al. (U.S. Patent No. 5,288,711, cited by Applicants, reference "Z") are directed to elements of the claimed subject matter which, when

combined, render the subject matter obvious, contrary to Applicants' assertion. Also, that Mitchell requires heparin is immaterial because the present claim recites "comprises" and thus does not preclude other active agents.

II Claims 22, 24 and 25 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 14 of U.S. Patent No. 6,432,973, (Zhu et al., cited by the Examiner), which has a common assignee with the present application, in view of Wright et al. (U.S. Patent No. 6,585,764, cited by the Examiner) and Mitchell et al. (U.S. Patent No. 5,288,711, cited by Applicants, reference "Z"), each of record, for the reasons set forth in the previous Office action at page 10-12.

Applicant's Arguments

Applicants' arguments are the same as presented *supra*. In response, the Examiner incorporates his reasons why the rejection is proper here by reference thereof.

None of the claims are allowed.

THIS ACTION IS MADE FINAL. Applicants are reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Raymond J. Henley III whose telephone number is 571-272-0575. The examiner can normally be reached on M-F, 8:30 am to 4:00 pm Eastern Time.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Raymond J Henley III
Primary Examiner
Art Unit 1614

December 14, 2005